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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/765,026	01/13/97	BARKATS	ST94051-US

M
EXAMINER

18N2/0102

GROUP ART UNIT	PAPER NUMBER
1805	6

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DATE MAILED: 01/02/98

This is a communication from the examiner in charge of your application.
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OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 1/13/97

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire Three (3) month(s), ~~or thirty days,~~ whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 29-60 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 29-60 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☑ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☑ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☑ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). 3
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

* U.S. GPO: 1996-404-496/40517

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

2. Claims 29-34, 38- 40, 43, 45, 48 and 50-54 are rejected under 35 U.S.C. 102(e) as being anticipated by Greenberger (U.S. Patent 5,599,712).

Applicants claim replication defective adenoviral vectors capable of expressing a superoxide dismutase gene product (i.e. human CuZn superoxide dismutase) wherein the superoxide dismutase gene is under control of a promoter (i.e. a viral promoter) which can be expressed in target cells, cells containing said vectors and pharmaceutical compositions comprising said adenoviral vectors.

Greenberger (See whole document, particularly Figs. 3a-3b, the paragraph bridging Columns 5-6, Columns 7-8, paragraph bridging Columns 11-12, Columns 13 and 16) teaches the generation of replication defective adenoviral vectors capable of expressing human superoxide dismutase genes (i.e. MnSOD or CuZnSOD, etc. derived from genomic or cDNA sources) wherein the SOD gene is under control of a viral (i.e. the adenoviral MLP) promoter, human cells which are be infected with said vectors, and pharmaceutical compositions comprising said vectors (at dosages of 10^6 to 10^{14} PFU/ml). Therefore, Greenberger teaches the claimed invention.

3. Claims 29-31, 33, 38, 48, 50, 53, 54 and 55 are rejected under 35 U.S.C. 102(e) as being anticipated by Ohno et al. (U.S. Patent 5,571,797).

Applicants claim replication defective adenoviral vectors capable of expressing SOD sequences wherein the SOD coding sequence is under control of a promoter which is expressed in target cells, pharmaceutical compositions comprising said vectors and mammalian (i.e.. human) cells containing said vectors.

Ohno et al. (See whole document, particularly Columns 2, 13, 22, 23, 29-31 and Table 3) teaches the generation of replication defective adenoviral vector capable of expressing a human MnSOD gene under the control of a promoter active in target cells, pharmaceutical compositions comprising said vectors and a variety of human cells which can be infected with these vectors so as to treat the human diseases outlined in Table 3.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor

and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 41, 42 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Greenberger in view of Engelhardt et al. and Kaufman.

Greenberger (U.S. Patent 5,599,712), is cited as in the above 102(e) rejection. Greenberger does not recite the generation of adenoviral vectors containing non-functional E2, E4, etc. genes and does not recite the use of a RSV-LTR promoter in said vectors.

Engelhardt et al. (PNAS, Vol. 91, June 1994, pp. 6196-6200, see whole article, particularly the Abstract and last three paragraphs of the Discussion) teaches the use of adenoviral vectors containing a non-functional E2 gene. It is noted that PNAS Volume 91 was received in the U.S. Patent Office Biotechnology Library on June 27, 1994.

Kaufman (Methods in Enzymology, Vol. 185, 1990, pp. 487-511, see whole article, particularly pp. 496-497) teaches the well known use of one of the most well characterized viral promoters (the RSV-LTR) in expression vectors of choice.

Greenberger teaches the basic aspects of the claimed invention absent the choice of the specific promoter (RSV-LTR) to be used in expressing the SOD gene and the inactivation of the adenoviral E2 gene. Since the RSV-LTR is one of the most well known viral promoters and is routinely used in expression vectors and since Engelhardt et al. teaches the desirability of using adenoviral vectors wherein the E2 gene is non-functional, it must be considered that the ordinary

skilled artisan, seeking to generate an adenoviral vector for the expression of SOD, would have been motivated to use one of the most well known viral promoters (the RSV-LTR) and use an adenoviral vector wherein the E2 gene is non-functional for the express, art recognized, desirability of using these promoters and vectors (i.e. using a well known promoter and an adenoviral vector construct desirable for use in gene therapy). It would have been obvious for the ordinary skilled artisan to use an adenoviral construct lacking a functional E2 gene because of the desirability (as disclosed by Engelhardt et al.) of using such a vector for gene therapy and to use the RSV-LTR to express the SOD gene because this is one of the most well known and routinely used promoters for expression of heterologous genes in expression vectors. Given the teachings of the cited prior art references and absent evidence to the contrary, it must be considered that the claimed invention would have been *prima facie* obvious to the ordinary skilled artisan and that said artisan would have had a reasonable expectation of success in practicing the claimed invention.

6. Claims 46, 47 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Greenberger in view of Erzurum et al.

Applicants claim a method (and pharmaceutical composition) for treating or preventing a disease characterized by an excess of free radicals by administering a pharmaceutical composition comprising a replication defective adenovirus vector capable of expressing a SOD and optionally a catalase.

Greenberger (Cited above, see whole article, particularly Columns 2-3 and Claims 1-25) recites the generation of replication defective adenoviral vectors capable of expressing human SODs and use of said vectors to reduce the levels of oxidant injury caused by an excess of free radicals in cancer patients undergoing ionizing radiation or chemotherapy treatments. Greenberger does not recite use of the catalase gene to reduce oxidant injury.

Erzurum et al. (Cited by applicants, see whole article, particularly the Abstract and Discussion section) recites the use of recombinant replication defective adenovirus vectors to express a catalase gene in cells so as to reduce the level of oxidant injury, particularly that mediated by H_2O_2 in patients.

The ordinary skilled artisan, seeking to develop a method and pharmaceutical composition for treating diseases caused by oxidant injury resulting from an excess of free radicals, would have been motivated to use the teachings of Greenberger on the development of replication defective adenoviral vectors which express a human SOD gene so as to reduce the levels of free radicals in cancer patients undergoing radiation or chemotherapy treatment combined with the teachings of Erzurum et al. on the use of replication defective adenoviral vectors to deliver and express a gene (such as the catalase gene) which protects cells from oxidant injury in order to use replication defective adenoviral vectors to express a SOD gene product which reduces, in patients, oxidant injury resulting from excess free radicals wherein the patient suffers from a disease where excess free radicals are a problem. It would have been obvious for the ordinary skilled artisan to do this because Greenberger teaches the desirability of using expression of the SOD gene product to

reduce the level of cell damage resulting from excess free radicals and because Erzurum et al. teaches that adenoviral vectors capable of expressing genes (such as catalase) which reduce cell damage by oxidants could be used to treat patients suffering from diseases where oxidant injury is a problem. Given the teachings of the cited references, it must be considered that, absent evidence to the contrary, the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

7. Claims 56-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Greenberger in view of Erzurum et al., Gage et al. and Naughton et al.

Applicants claim an implant comprising cells containing replication adenoviral vectors capable of expressing SOD genes and extracelluar matrices comprising gelling compounds for support of the cells and wherein the support also comprises polytetrafluoroethylene fibers.

Greenberger and Erzurum et al. are cited as in the above 102(e) and 103 rejections. Neither Greenberger nor Erzurum et al. recite the use of implants comprising virus infected cells to deliver pharmaceutical compounds or compositions to patients.

Gage et al. (Cited by applicants, see whole article, particularly pp. 24-26 and Claims 1-28) recites the therapeutic use of implants comprising genetically modified retroviral infected cells and a gelling compound for cellular support.

Naughton et al. (U.S. Patent 4,963,489, issued 10/16/90, see whole document, particularly Claim 7) recites the use of polytetrafluoroethylene as a non-biodegradable support for cellular implants.

The ordinary skilled artisan, seeking to develop implants for treatment of diseases characterized by an excess of free radicals, would have been motivated to use the teachings of Greenberger and Erzurum et al. on the development of replication defective adenoviral vectors capable of expressing SOD genes for treatment of diseases characterized by oxidant damage and further combined with the teachings of Gage et al. and Naughton et al. on the use of implants comprising extracellular support matrices (i.e. gelling compounds or polytetrafluoroethylene) compounds to reliably deliver therapeutic compositions to patients in order to deliver the adenoviral vector encoded SOD gene products to patients by means of cellular implants comprising standard extracellular supports such as collagen or polytetrafluoroethylene. It would have been obvious for the ordinary skilled artisan to do this because the use of implants to deliver therapeutic products produced from viral infected cells expressing a transgene was well known in the art (See Gage et al.) and the use of extracellular supports such as collagen or polytetrafluoroethylene to support the cellular implants were standard in forming the implant. Given the teachings of the cited references and absent teachings to the contrary, it must be considered that the skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

8. Claims 35-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants claim recombinant replication defective adenoviruses encoding sequences (i.e. dominant negative mutants, antisense sequences, etc.) designed to control or down-regulate production of SOD. The claimed invention is not enabled however for the following reasons: 1) Applicants have not disclosed any particular condition (disease or otherwise) in which the claimed vectors could be used. This is important because lack of information on any specific condition which is to be treated makes it impossible to determine whether the claimed invention is enabled. For example, if the condition or disease to be treated is chronic in nature, expression of the transgene or antisense sequence would need to be prolonged to provide some treatment; alternatively, if the condition is acute, then short term expression of the heterologous sequence may be sufficient. If long term expression is desired, significant problems associated with prolonged expression of transgenes in vivo remains an unsolved problem (See Orkin et al. and Verma et al., Nature, Vol. 389, 18 Sept. 1997, pp. 239-242, see whole article, particularly pages 239 and 241) in the gene therapy art. Also, given the absence of any teachings on specific conditions to be treated with the claimed invention, it is unclear what levels of heterologous sequence expression would be desirable.

2) Applicants provide no teachings on what type of promoters are to be used to express the sequences which regulate SOD production; i.e. are inducible promoters desirable, are constitutive promoters desirable?

3) Applicants provide no teachings on how the skilled artisan would regulate the expression of endogenous SOD production in patients. For example, if the level of suppression of SOD by the antisense or dominant negative mutant sequence is too great, the resulting excess of free radicals could cause the very diseases (i.e. neoplasms, inflammation, diabetes, etc.) which applicants seek to treat by over expressing SOD through introducing adenoviral vectors capable of expressing exogenous SOD.

4) Applicants provide no working examples of the claimed invention.

Given the lack of guidance by applicants on how the skilled artisan would make **and use** the claimed invention and given the essential nature of the missing information, the skilled artisan would essentially have had to have practiced trial and error experimentation in order to attempt to practice the claimed invention. This type of experimentation is the antithesis of enablement under 35 USC 112, 1st paragraph and said experimentation must be considered to be undue and excessive.

9. Claims 46-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of **treating** diseases characterized by an excess of free radicals, does not reasonably provide enablement for **preventing** said diseases. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

Applicants claim a method for preventing (i.e. immunizing individuals against) diseases such as cancers, diabetes, Alzheimer's disease, ALS, etc. However, the instant specification does not contain a disclosure sufficient to enable a method of immunizing or vaccinating an individual against diseases as varied as cancer, diabetes, hypertension, ALS, etc. Indeed, no art exists on any recombinant or gene therapy methods of immunizing or treating individuals **in order to prevent** said individuals from acquiring cancer, diabetes, ALS, hypertension, etc. and applicants provide no teachings on how the skilled artisan would develop or administer the claimed invention so as to prevent an individual from acquiring these diseases. Also, to prevent diseases (such as neoplasms, hypertension, cirrhosis of the liver, etc.) which often take years to develop, it would appear that expression of the SOD gene sequences would need to be prolonged in order to provide an individual with protection; however, it is again noted that prolonged expression of introduced genes in a gene therapy context has not been achieved (See Verma et al.) and it is noted that multiple treatments with adenoviral vectors often results in severe immunological reactions against the vector and cells infected with the vector in patients. Applicants also provide no guidance on the level of expression of the SOD gene which would be sufficient to prevent a disease such as hypertension or ALS vs. a disease such as cardiovascular disease, etc. Would the level of expression of the SOD gene sufficient to prevent an individual from developing cancer be sufficient to prevent an individual from acquiring hypertension? Applicants provide no guidance

on these issues which are essential for practicing the claimed invention. It is also noted that the underlying mechanisms for the extremely wide range of diseases which are to be prevented are diverse and often unrelated and therefore it is unclear how merely expressing exogenous SOD (which treats only one factor in a complex series of events which often underlies a disease such as hypertension or cancer) would **prevent** an individual from acquiring hypertension or ALS or diabetes or cirrhosis of the liver, etc. Also, would not the expression of exogenous SOD in an individual for a period of time produce high levels of SOD and result in negative effects from the presence of excess hydrogen peroxide?

Given the complex nature and wide variety of diseases to be prevented, given the lack of guidance on how any particular disease is to be prevented, given the extremely complex and unpredictable nature of the gene therapy art, given the unprecedented nature of applicants' claims, given the lack of any working examples and given the absence of any practical guidance on how the skilled artisan would design and administer any particular adenoviral vector to treat any particular disease, it must be considered that the skilled artisan would have had to have practiced trial and error experimentation in order to try to practice the claimed invention. This type of experimentation is the antithesis of enablement under 35 USC 112, 1st paragraph and must be considered to be undue and excessive.

10. Claims 44, 48 and 50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 44 is vague because it depends from canceled claim 13.

Claims 48 and 50 are vague in that they can be read to claim a composition comprising one replication defective adenovirus. A composition claim must recite two or more components since a composition inherently cannot consist of only one element.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo whose telephone number is (703) 308-1906. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached on (703) 308-4003. The fax phone number for this Group is (703) 308-4242 or (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

David Guzo
December 29, 1997

DAVID GUZO
PRIMARY EXAMINER
GROUP 1800